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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61L 31/00

A1

(11) International Publication Number: WO 94/21309

(43) International Publication Date: 29 September 1994 (29.09.94)

(21) International Application Number: PCT/BE94/00024

(22) International Filing Date: 24 March 1994 (24.03.94)

(30) Priority Data:
9300285 24 March 1993 (24.03.93) BE

(71) Applicant *(for all designated States except US)*: N.V. D.S.B. [BE/BE]; Meirbrug 1, Bus 2, B-2000 Antwerp (BE).

(81) Designated States: AU, BG, BR, CA, CN, CZ, HU, JP, NZ, PL, RO, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: POLYURETHANE-COATED INTRAVASCULAR PROSTHESES (STENTS) FOR THE TREATMENT OF BLOOD VESSEL STENOSIS

(57) Abstract

A new method to treat blood vessel stenosis using endovascular prostheses which are coated with amphiphilic polyurethanes to which medicines can be coupled. By coating endovascular prosthesis with amphiphilic polyurethanes, we have succeeded in significantly improving the bio- and bloodcompatibility of endovascular prostheses. These amphiphilic polyurethanes have the property, when implanted in human or animal tissue and blood vessels, of remaining stable and seeming not to provoke an inflammatory reaction. Furthermore it is possible to incorporate medicines in these polymers which, after implantation of the polymers, are slowly released at the location of the place of implantation. This system can further reduce the thrombogenicity of the prostheses coated with the polyurethanes and inhibit the rejection against these prostheses.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE 94/00024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 1 is directed to a method of treatment of the human/animal body the search has been carried ot and based on the alleged effects of the product."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0518704	16-12-92	JP-A-	5200048	10-08-93
WO-A-8704935	27-08-87	DE-A-	3786721	02-09-93
		EP-A,B	0257091	02-03-88
		EP-A-	0556940	25-08-93
		US-A-	4768507	06-09-88
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EP-A-0566245	20-10-93	JP-A-	6007455	18-01-94
US-A-4371686	01-02-83	JP-C-	1184116	27-12-83
		JP-A-	57051718	26-03-82
		JP-B-	58008700	17-02-83

POLYURETHANE-COATED INTRAVASCULAR PROTHESES (STENTS) FOR THE TREATMENT OF BLOOD VESSEL STENOSES. A new method to treat blood vessel stenoses by means of endovascular protheses which are coated with amphiphylic polyurethanes to which medicines can be coupled.

DESCRIPTION

Treatment of blood vessel stenoses by means of a balloon catheter is a popular method. Last year, more than 6,000 patients with coronary heart disease were treated by this method in our country. The problem with this method is on the one hand the danger that a tear occurs during the blowing up of the balloon whereby the blood vessel can close and thus cause an acute myocardial infarction, on the other hand it is well documented that this treatment method is accompanied by a frequent restenosis of the treated blood vessel within 6 months of the treatment. To solve this problems, medicines were tested in order to prevent the restenosis and furthermore new devices were developed. One of these new methods consist of placing a metal intravascular prothesis (stent) at the level of the vessel stenosis. This method is very efficient for treating vessel tears which can occur during balloon dilatation. The problems with this metallic stents however are that they have proven to be thrombogenic and can cause an acute thrombotic occlusion of the treated blood vessel. On the other hand, it appeared that through the inplantation of a metal stent in a blood vessel, the body can react with an inflammatory reaction whereby restenosis within the stent can occur. By covering these endovascular protheses with amphiphylic polyurethanes, we succeeded in significantly limiting both the problem of trombogenecity as well as the problem of reactive hyperproliferative response.

Amphiphilic polyurethanes were synthesized starting from amphiphilic polyester diols on the basis of ethylene oxide and proylene oxide. By reaction with a diisocyanate and a chain lengthener (butanediol), a thermoplastic polyurethane is finally obtained. By the appropriate choice of a) the polyesterdiol, especially the proportion of ethyleneoxide/propyleneoxide, and b) the molecular weight of the diol, the bio- and blood compatibility can be optimized. Furthermore the kind of sterilisation of polyurethane-coated devices turned out to be very critical. We used certain amounts of gamma radiation which resulted in the formation of further crossbridging of the polymer leading to a more stable and more elastic polymer which is critical during the stent deployment. The resulting polymers turned out to be very stable when inplanted in human or animal tissues or blood vessels. Furthermore they did not provoke any inflammatory reaction.

Furthermore we were able to load these polyurethanes with medicines, which were released slowly at the polymer implantation side. These medicines are used to further decrease the thrombogenecity of the stents (heparin, hirudin, streptokinase, urokinase, tpa and other anticoagulants) and

to inhibit the inflammatory reaction caused by the stent (corticosteroids, antimitotics, angiopeptin and other antiinflammatoy drugs.) Using methylprednisolone loaded polyurethane coated stents we were able to block totally the stent restenosis in a pig coronary model.

APPLICATION POSSIBILITES OF THE SYSTEM

1. Treatment of blood vessel stenosis in humans and animals.

2. Treatment of complications occurring during other treatment methods of blood vessel stenosis.

3. Treatment of complications occurring during diagnostic procedures.

4. Coating of prosteses, wires, and catheters introduced for medical purposes.

CLAIMS

By coating endovascular protheses with amphiphylic polyurethanes, we have developed an efficient method to treat blood vessel stenosis. This method proved to considerably limit the thrombogenicity as well as the rejection against endovascular protheses so that this method signifies an important step forward in the treatment of blood vessel stenosis.

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